(Privileged Communication)

Application Number: 1 R01 ES01976-01
Dual Review: CA

Review Group: PATHOLOGY - B SS
Meeting Date: FEB/MARCH 1978 (AHR)

Investigator: LEDERBERG, JOSHUA Degree: PHD
Position:

Organization: Rockefeller University
City, State: New York, New York Requested Start Date: 07/01/78

Project Title: ENVIRONMENTAL HEALTH ASPECTS OF CARBON

Recommendation: APPROVAL Priority Scor
Special Note:

NO HUMAN SUBJECTS
NO RECOMBINANT DNA RESEARCH IS INVOLVED

PROJECT YEAR	DIRECT COSTS REQUESTED	DIRECT COSTS RECOMMENDED	PREVIOUSLY RECOMMENDED	GRANT PERIOD
01	293,516	103,199		
02	175,167	103,299*		
03	190,760	103,399*		
04	207,844	103,499*		

*Not adjusted for annual salary and/or cost of living increases

RESUME: Approval at a reduced budget is recommended for this application. Development and application of methods for the detection and mutagenicity testing of potential carcinogens adsorbed or bound to polymeric carbon in the environment are proposed. The application is primarily technological and suffers from conceptual shortcomings. Its goals can be achieved but there are reservations about the significance and/or utility of the information to be obtained.

DESCRIPTION: This is a new application that proposes to develop and apply methods for the detection of potential carcinogens that are either adsorbed or chemically bound to various forms of polymeric carbon contaminating our environment. Biologically active, organic compounds could be associated with polymeric carbon in three separate processes; (1) the high surface area of polymeric carbon makes it an excellent adsorbent surface; (2) the surface carbon atoms may be oxidized leading to the generation of a variety of surface bound carboxylic and phenolic derivatives; and (3) the extensive adsorbing surfaces of polymeric carbon may act as a catalyst for a number of chemical reactions. Studies are proposed that deal initially with commercially available carbons (e.g., Tampblack from Fisher Chemical Co.,). The initial objective is the development of methods for the isolation and identification of compounds present through each of the above 3 mechanisms. Greatest attention will be given to the analysis of adsorbed aromatic hydrocarbons. Initially, solvent extraction procedures will be optimized using the commercially available polymeric carbons and added radiolabeled benzo(a)pyrene. Benzene, naphthalene and phenanthrene will be employed as solvents. Combined gas chromatography/mass spectrometry (GC/MS) will be used to determine quantitative data on the extractability of this polynuclear hydrocarbon. The perfected methodology will then be applied to the isolation and identification of similar compounds naturally adsorbed to a number of commercially available carbons. Preliminary studies reported in the application have identified a number of different compounds extracted by benzene and naphthalene from lampblack and Degussa Special Black 5. A number of aromatic hydrocarbons were identified in the extract of lampblack.

No definitive identifications of known polynuclear aromatics (PNA's) were made on the extract from the Degussa Black. Further development of the extraction procedures as outlined above and the application of more sensitive mass spectroscopy and high pressure liquid chromatography is proposed in the identification of the extractable compounds adsorbed to these commercial carbons. Eventually, application of these methodologies to the study of polymeric carbons of environmental origin, e.g., soot from coal combustion, is proposed. Concurrent with the actual chemical isolation and identification of adsorbed substances, it is proposed to evaluate the mutagenicity of the extractable materials by application and refinement of the Ames test and the development of new systems that may have greater sensitivity based on bacteriophage genotypes that are internally self-repressed but which will break through if they experience any of a range of mutational events. No other details are given. Specific procedures are given for the analysis of the catalytic activity of polymeric carbon surfaces and for the identification of bound oxidation products. Specific carbon samples from commercial sources will be subject to mild and to vigorous oxidation conditions and the products obtained identified by GC/MS. The ability of well characterized polymeric carbons to catalyze the oxidation of known PNA's to proximate carcinogens will be studied.

CRITIQUE: This is a wandering application in which a great many specific experiments are proposed and from which it is somewhat difficult to extract the specific sequence of studies to be performed. The main thrust of the proposal is the extraction, isolation, identification and mutagenicity screening first of complex organic compounds adsorbed to specific forms of polymeric carbon commercially available and then from carbon sources of potential significance as human health hazards. The major rationale of the study is the possibility, amply sustained by Dr. Lederberg's preliminary studies, that polymeric carbons from a variety of commercial and environmental sources will be shown to carry a number of specific compounds of potential biological significance. This possibility does not appear to justify the level of support requested. There appear to be no known epidemiological data to suggest that exposure to chemicals contaminating polymeric carbons produced and released into the environment in abundant quantities by natural and man-made processes is causally related to human malignancies. This question is not addressed by Dr. Lederberg. Begging this issue and even assuming that the contamination of our environment with carcinogen bearing polymeric carbons is a real health hazard, will the isolation and identification of specific mutagens from these sources advance the control of the cancers they may possibly induce? This is a complicated question. Obviously it will not be possible in the near future to rid our environment of these ubiquitously present contaminants. The identification of the particular compounds that are responsible for the observed biology is not, it would seem, a particularly useful way to tackle the problem of controlling and eliminating environmentally related cancers.

The proposal offers a very sophisticated approach to evaluating the hazard of "polymeric" carbon. Much of the proposal relates to the development of technology to assay complex mixtures which may contain carcinogenic compounds. It is anticipated that a number of compounds will be discovered and quantitiated. It would appear that each lot or type of "polymeric" carbon might have a number of technical problems associated with it regarding chemical definition and testing for mutagenesis.

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A more readily controlled approach might be to choose for analysis several known sources of carcinogenic PNA fractions such as coal tar or oil shale reaction mixtures where high hazard to workers is anticipated. The charcoal preparations do not appear, a priori, to be great hazards but coal tar and shale oil mixtures which have been treated to remove natural gas or crude oil are potential environmental hazards.

This proposal appears to be far stronger in its technology than in its concepts. As it is written, it tends to belie a poor grasp of the problem and an inadequate analysis of existing data. Determination of individual structures of trace level compounds is extremely difficult. For example, Drs. Lederberg and Smith state, "... this compound may be dinaphthofuran". Which of the several isotopes is it? How will other structures be determined? There is no obvious correlation between hydrocarbons adsorbed to environmental carbon and that in "commercial carbon blacks" with their infinite variety of components. Oxidation to arene carboxylic acids would seem to be of little value as it could arise from core matrix or from adsorbed compounds.

It is difficult, therefore, to approve with much enthusiasm the present proposal. It seems certain that Dr. Lederberg will accomplish successfully his objectives with the generation, through a great deal of effort, a large mass of specific data relative to the issue at hand here. There is disagreement with the approach to the problem that this application represents and, therefore, there are reservations about the significance and/or usefulness of the information to be obtained.

INVESTIGATORS: Joshua Lederberg (Ph.D., 1947, microbiology, Yale University) will assume the Presidency of Rockefeller University on July 1, 1978. He proposes to continue as the principal investigator of this project, which will become his major research interest. Much of the specific direction of the project will be under the direction of Dr. Lederberg's associate, Dennis Smith (Ph.D., 1967, chemistry, University of California, Berkeley). Dr. Smith will accompany Dr. Lederberg to New York and will ultimately assume complete responsibility for the project. He has been a research associate at Stanford University since 1971. He has published 42 papers with a variety of collaborators dealing with various aspects of organic chemistry. The remaining personnel will be new.

RESOURCES AND ENVIRONMENT: Generally it would seem that the facilities in the new environment will approximate quite closely those currently existing at Stanford. Dr. Lederberg has permission to transfer much of his equipment. The environment at Rockefeller University appears excellent.

BUDGET: The requested budget is very large, and definitely excessive, particularly in the light of the amount of preliminary data obtained without such expenditures. The personnel budget should be reduced to include Dr. Smith ($33,404), one research associate ($22,906) and one technician ($15,509). Again, based on the preliminary data, support for the new GC/mass spectrometer and accompanying computers is not justified and their funding is deleted ($111,150). There is a need for the HPLC. Thus, the equipment budget is reduced to $18,580. In light of these reductions, the supplies budget requested is considered excessive and is reduced to $8,000 per year.

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There is no justification for the $20,000 for engineering services requested under Other Expenses and the maintenance contract for computers ($8,400) is not required, so Other Expenses is reduced to $3,800 per year. Similar reductions apply in the 2nd through 4th years.